wherein said polypeptide bound to said HLA-DR protein activates autoreactive T cells from a subject having said autoimmune disease; and

wherein said polypeptide is a non-collagen and non-myelin basic protein polypeptide.

13. A pharmaceutical preparation for vaccinating an individual at risk of an autoimmune disease comprising a pharmaceutically acceptable carrier and

an amount of an immunogenic preparation effective to immunize against a human pathogen that in its native form includes a polypeptide having an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein;

wherein said sequence motif for an HLA-DR protein is based upon the structure of the HLA-DR binding site

wherein said HLA-DR protein is associated with said autoimmune disease;

wherein said polypeptide binds to said HLA-DR protein;

wherein said polypeptide bound to said HLA-DR protein activates autoreactive T cells from a subject having said autoimmune disease; and

wherein said preparation is free of a polypeptide corresponding to said sequence.

RESPONSE

Claims 3-19 and 22 were pending in the Application. In a Response to a Restriction Requirement filed on April 8, 1999, Applicants elected to pursue prosecution of the claims of Group I. Upon entry of the present amendment, claims 3 and 13 are amended, and claims 7-10, 12, 17-19 and 22 are cancelled. Applicants submit that no new matter is added by the present amendment. Support for the amendments to claims 3 and 13 may be found in the Specification, for example, at page 19, line 16 through page 23, line 14, where techniques for developing an HLA-DR binding motif are taught. Further support for the amendments to claims 3 and 13 may

be found in the Specification, page 52, lines 25-30, where the term "core MHC binding residues" is defined.

Identification of Claims Embracing the Elected Species

The Office Action required the Applicants to point out which of claims 3-19 and 22 embrace the elected species of SEQ ID NO.: 3. Clams 7-10, 12 and 17-19 and 22 have been cancelled by the present amendment. All of the remaining claims under consideration following entry of the present amendment (i.e., claim 3-6, 11, 13-16, 20, and 21) embrace the elected species.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 3-19 and 22 were rejected under 35 U.S.C. §112, first paragraph, as failing to meet the enablement requirement. The Office Action suggests that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In particular, the Office Action suggests that one of skill in the art would not have a reasonable expectation of inducing tolerance to PV using the peptide of SEQ ID NO:3 for the following reasons:

(1) Immunization of an individual with an HLA DRB1*0402 background with the epitope of SEQ ID NO.: 3 might be expected to cause antigen presenting cells to present an autoepitope of SEQ ID NO.: 3 to the individual's T cell population, thus expanding and activating autoreactive T cells and exacerbating PV rather than tolerizing and inhibiting PV.

(2) While the peptide of SEQ ID NO.: 3 was identified by the putative binding motif for DRB*0402, there is no evidence of record that this peptide in fact binds to DRB1*0402.

The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976).

A skilled artisan would have a reasonable expectation of inducing tolerance using the peptides of the present invention.

Applicants submit that methods for inducing tolerance to a potential antigen were known and practiced by those skilled in the art at the time the application was filed. It was recognized at the time of the invention that certain routes of administration of an antigen could promote the induction of immunological tolerance. For example, Critchfield (1994) Science, Vol. 263:1139-1142 (Attached as Exhibit A), reported that "high doses of antigen can paradoxically suppress immune responses in adult animals." Critchfield stated, at page 1140-1141, that "repeated intravenous treatments with large amounts of soluble MBP could delete peripheral autoreactive T cells and thereby improve the course of EAE." Similarly, Mowat (1987) Immunology Today, 8(3):93-97 (Attached as Exhibit B), reported that ingestion of an antigen could induce tolerance. Mowat stated, at page 97, that "the usual result of meeting a protein antigen by the oral route is the induction of specific immunological tolerance." In a further example, Briner, (1993) Proc. Natl.Acad. Sci., 90:7608-7612 (Attached as Exhibit C), reported that subcutaneous administration of an antigen induced tolerance.

US Patent No. 5,114,844 (Attached as Exhibit D), which issued to Cohen et al. on May 19, 1992, described the induction of tolerance by administration of an autoantigenic peptide by injection. Cohen emphasized that proper selection of the carrier used in administration by injection could result in tolerization. Cohen reported that "it is well established that antigen administered without an effective adjuvant, or with a tolerogenic carrier, can induce immunological non-responsiveness, *i.e.*, specific tolerance to the antigen." (Column 11, lines 45-48) Cohen provides examples of tolerogenic carriers at column 14, lines 4-7.

Furthermore, successful immunotolerization to an autoantigen has been demonstrated in a variety of experimental autoimmune disorders. Weiner (1994) Annu. Rev. Immunol. 12:809-37 reported, at page 823, lines 7-11 (Attached as Exhibit E), that "[o]rally administered autoantigens suppress several experimental autoimmune models in a disease- and antigen-specific fashion; these diseases include experimental autoimmune encephalomyelitis (EAE), uveitis, and myasthenia, collagen- and adjuvant-induced arthritis, and diabetes in the NOD mouse. ... Initial clinical trials of oral tolerance in multiple sclerosis, rheumatoid arthritis, and uveitis have demonstrated positive clinical effects with no apparent toxicity and decreases in T cell autoreactivity."

Applicants submit that methods of inducing immunotolerization were known in the art at the time the application was filed. Moreover, Applicants respectfully note that a specification need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987). Consequently, Applicants submit that a regurgitation of prior art immunotolerizing techniques in the Specification is unnecessary, and that one skilled in the art, upon reading the Specification, would not require more than reasonable experimentation to practice the invention.

In light of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C §112, first paragraph, be reconsidered and withdrawn.

A skilled artisan would have a reasonable expectation that the peptides of the present invention would bind to an autoimmune associated HLA-DR protein.

In order to make an enablement rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph,

unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. As stated by the court in *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971), "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 169 USPQ at 370. MPEP 2164.04

The Office Action relies on O'Sullivan et al. (1991) to support the proposition that the peptides of the invention could not be reasonably expected to bind MHC Class II DR molecules, as claimed. O'Sullivan disclosed a three-residue binding motif based upon sequence homology of peptides known to bind various HLA-DR alleles. In contrast to O'Sullivan, Applicants disclose and claim a binding motif based upon an analysis of the actual structure of the MHC Class II binding site. Applicants note that the binding motif of the present invention characterizes eleven residues of a putative binding peptide, five MHC contact residues and six T cell receptor contact residues. Consideration of the actual structure of the MHC Class II binding site provides a basis for applying the stereochemical and electrochemical limitations of candidate amino acid residues to the binding motif.

Applicants further note, as discussed in the instant Specification at page 13, lines 22-26, that a sequence motif, such as O'Sullivan's, based upon pure sequence homology with unlimited "conservative" substitutions, may admit "many peptides which differ at critical highly conserved sites" and, therefore, incorrectly predict binding. The differences in the bases for the motif of O'Sullivan and the motif of the present invention, namely (1) pure sequence homology versus structural analysis of the MHC binding pockets, and (2) the number of residues considered, clearly distinguish the binding motif disclosed by the Applicants in the instant application from the motif presented in O'Sullivan.

Applicants respectfully submit the ability or inability of the motif presented in O'Sullivan to predict peptide binding to MHC Class II DR molecules does not provide sufficient reason to doubt that the preparations recited in pending independent claims 3 and 13 would not bind to an HLA-DR protein. Therefore, Applicants submit that the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention has not been meet.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

Rejections Under 35 U.S.C. §102

Claims 3-19 and 22 were rejected under 35 U.S.C. §102 as being anticipated by Amagai et al., (1991) Cell 67:869-877. In particular, the Office Action suggests that that the claim language "consisting essentially of" does not exclude the full-length autoantigen for pemphigus vulgaris disclosed in Amagai.

Independent claims 3 and 13 are herein amended to recite, in part, "an isolated human polypeptide effective for tolerizing an individual to an autoantigen, said human polypeptide consisting essentially of an amino acid sequence corresponding to the core MHC binding residues of a sequence motif for an HLA-DR protein" (emphasis added).

According to the MPEP, the term "consisting essentially of" limits that scope of a claim to the "specified materials or steps and those which do not materially affect the basic and novel characteristic(s) of the claimed invention." (MPEP 2111.03) The disclosed invention provides a binding motif to determine which residues of a putative antigenic protein are the core MHC binding residues, and which peptides are capable of binding autoimmune associated HLA proteins. Accordingly, a basic characteristic of the disclosed and claimed invention is the ability to include the core binding residues (along with intervening residues and de minimus neighboring residues) and exclude other residues of a putative antigenic protein. Independent

claims 3 and 13 are intended to embrace polypeptides capable of binding autoimmune associated HLA proteins, not a full-length autoantigenic protein as discussed in Amagai.

Applicants submit that inclusion of the full-length 103 kD pemphigus vulgaris antigen protein disclosed by Amagai in the preparations of claim 3 would materially affect the basic and novel characteristics of the preparation and, therefore, the full-length pemphigus vulgaris protein is not included in the scope of independent claim 3. Applicants further submit that one of ordinary skill in the art would readily recognize that a preparation for tolerization consisting essentially of an isolated antigen binding peptide is superior to a preparation containing a full-length protein. For these reasons, Applicants submit that Amagai does not anticipate claims 3-6, and 11, as amended herein.

Furthermore, Applicants submit U.S. Patent No. 5,874,531 (the '531 patent), as evidence that pending claims 3-6, 11, and 13-16 are not anticipated by Amagai. Applicants note that the '531 patent is the parent of the instant application and that Claim 1 recites, in part, "an isolated polypeptide consisting essentially of an amino acid sequence selected from the group consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ ID NO.: 6, and SEQ ID NO.: 7." The Examiner in the '531 patent considered Amagai and found the invention recited in claim 1 to be novel over Amagai. Therefore, Applicants submit that at least claims 6 and 16 (if not all of the pending claims) of the present application are presumptively patentable over Amagai.

Applicants further submit that Amagai fails to anticipate pending claims 13-16 for the following reason. Independent claim 13 recites, in part, a vaccination preparation "that in its native preparation includes a polypeptide having an amino acid sequence corresponding to a sequence motif for an HLA-DR protein ... wherein said preparation is free amino acid sequence corresponding to a sequence motif for an HLA-DR protein." Amagai fails to teach a vaccination preparation which includes antigenic polypeptides of a pathogen and excludes polypeptides that activated autoreactive T cells from a subject having an autoimmune disease. Thus, Amagai does not anticipate these claims.